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Clinical Evaluation of Anemia

THE INTRODUCTION of electronic counting of blood cells into the routine clinical laboratory has been the greatest single advance in the routine laboratory evaluation of anemias since the introduction of the polychrome stains. The report of the modern complete blood count (CBC) contains a dazzling array of numbers derived from the analysis of a drop or two of blood. Many hematologists would agree that the probable cause of most anemias is indicated by the CBC, sometimes supplemented by the reticulocyte count. A few hematologists, spiritual denizens of an earlier time, look at the stained smears, but their number (the hematologists, that is, not the smears) is diminishing. A doctrine promulgated in Boston states that the examination of blood smears may safely be left to technologists, freeing hematologists for more profitable, if not more pleasurable, pursuits.[1] This sharing of the diagnostic prowess between technologist and physician has had a long tradition; it should be clearly understood, however, that the hematologist or physician must be well acquainted with the skills and experience of technologists to whom so much is entrusted. It will not do for administrators to budget for housekeeping aids to replace physicians in examining blood smears.

Elsewhere in this issue of the journal, Ralph Wallerstein, Jr, MD, has written a lucid exposition of the modern laboratory evaluation of anemia. It seems probable that the heresy about the peripheral smear has adherents in San Francisco because Dr Wallerstein appears to rank examination of the stained smear below the CBC and reticulocyte count.

Although electronic counting yields an accurate enumeration of red blood cells and hemoglobin is directly and rather precisely measured, most physicians continue to speak of the hematocrit, a test that would rapidly join the icteric index were it not kept alive, and indeed nurtured, by physicians trained in ages past. Ask a medical student, or for that matter a medical resident, about a patient's red blood cell count and you are likely to see a look of utter disbelief, as though you had asked for Osler's home telephone number.

Red blood cells were probably first counted in 1852, when values of about 5 million per μl were obtained by Nierodt. Subsequently, inaccuracies in routine counting caused the red blood cell count to fall into disrepute, and it was replaced by the hematocrit in the evaluation of anemia. Electronic blood counting, however, with accurate red blood cell counts has been available in hospital laboratories for more than two decades, yet the red blood cell count is still largely ignored by many physicians.

Ironically, the more highly regarded mean corpuscular hemoglobin and mean corpuscular volume are dependent on the red blood cell count. One might speculate that had the red blood cell count never been done in clinical laboratories until electronic counting became available, it would have been accepted by clinicians with enthusiasm. Many years will apparently be required for the count to live down its shady past. Yet, a 25-year-old Laotian man with a hemoglobin of 12 grams per dl and 6.5 million per μl red blood cells probably needs only a hemoglobin analysis to complete the workup of his microcytic anemia.

The common diagnostic problem in the analysis of modestly microcytic anemias is the association with chronic disease; Dr Wallerstein has addressed this problem in helpful detail. To his list of causes of microcytic anemia, one might add pyropoikilocytosis, an admittedly rare disorder, but one in which the diagnosis may be overlooked for many years.

In the analysis of macrocytic anemias, most physicians do not have access to the deoxyuridine suppression test, and its usefulness in a clinical laboratory remains to be evaluated. The measurement of gastric hydrochloric acid receives little mention now, although it can be valuable in evaluating megaloblastic anemia, particularly with pentagastrin stimulation. The absence of hydrochloric acid in gastric contents does not provide a definitive test in the elderly, but its presence rules out pernicious anemia (with the implication of lifelong monthly injections of vitamin B_{12}).

The Schilling test may be the gold standard in the diagnosis of pernicious anemia, but its accuracy is uncertain in many laboratories. Some laboratories have not been able to substitute counting of plasma for urine unless the isotope dosage was increased, and incomplete urine collections are regularly blamed for any problems that are encountered.

Many drugs used in the treatment of malignant disorders cause megaloblastic anemias, some by directly interfering with DNA synthesis, while others are folic acid antagonists, usually inhibiting dihydrofolate reductase. Other drugs, particularly anticonvulsants, occasionally lead to megaloblastosis by poorly understood interference with mechanisms of gastrointestinal absorption. Oral contraceptives have been rarely associated with folic acid deficiency. In view of the numerical decline in options for contraception, the risk of folic acid deficiency in association with oral contraceptives ought to be more clearly delineated.

In the analysis of hemolytic anemias, Dr Wallerstein recommends looking for hemoglobinuria; the examination of stool specimens for blood might be recommended as an equally immediate test in evaluating microcytic anemias. It is also not clear that sickle cell anemia "is obvious from the smear" to everyone. Sickle cell preparations or solubility tests are far better.

This review appears shortly after publication of an article in another journal indicating that the evaluation of anemia was not very competent in a significant proportion of medical inpatients in a university hospital.[2] Dr Wallerstein's article obviously deserves a wide readership.

Another (also recent) article emphasizes the lack of efficacy of CBCs in detecting disease of healthy people.[3] Any elderly university hematologist who taught presumably healthy medical students to do CBCs (on themselves) would certainly agree. It is also not clear, however, that consultation with physicians is a cost-effective method of disease detection in a healthy population. Perhaps the role of physicians should not be the enthusiastic search for disease in asymptomatic

healthy people for whom preventive medicine seems more appropriate. Smoking cessation clinics may be a lot more useful than serial blood counts of the healthy population.

Dr Wallerstein provides a useful review of the laboratory approach to anemia that has already been detected. The *clinical* evaluation will often shorten the laboratory evaluation a great deal: evaluation of the anemia of an alcoholic patient, or of a patient with bacterial endocarditis, may often be deferred because the anemia will disappear when the underlying illness is cured. The ready availability of laboratory tests makes possible sophisticated evaluations that may be unnecessary. The array of tests in a clinical laboratory is one of the achievements of modern clinical science. The critical and discriminating use of those tests should be another achievement: in most cases of anemia, the clinical evaluation begun with the history and physical examination followed by the modern CBC may require only a few additional laboratory tests.

HELEN M. RANNEY, MD
Professor of Medicine
Department of Medicine
University of California, San Diego, School of Medicine
La Jolla

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Transient Ischemic Attacks

IN THIS ISSUE of the journal, Rothrock reminds us that transient ischemic attack (TIA) is an important risk factor for stroke. He also emphasizes that TIA is as important a warning of future myocardial infarction as of stroke, and that most persons who experience such an event do not suffer a subsequent stroke. Additionally, there is no ideal medical treatment for all TIAs, and surgical treatment is risky business. He argues that for these reasons, the often recommended aggressive approach to the evaluation and treatment of TIA should be restrained. Finally, Rothrock argues that TIA is a family of pathophysiologic disorders, each with its own natural history. Some TIAs are relatively benign while some warn of impending disaster. It follows that the aggressive use of high-risk therapy for benign TIA in an elderly patient with severe coronary artery disease is unwarranted. Alternatively, a nihilistic approach to a younger patient with a malignant TIA seems equally unwarranted. I agree generally with all of these assertions. I am less optimistic that we can determine the specific cause of most TIAs, and I am more optimistic about treatment.

Rothrock believes that much of our failure to demonstrate real benefit from various treatments for TIA and stroke has resulted from the tendency to lump together the diverse causes. There are indeed many causes of TIA and ischemic stroke, and I am a strong advocate for being clear in one's thinking and stringent in one's evaluation of patients in this regard. Nevertheless, the vast majority of TIAs occurring in elderly persons in western countries are caused by obstruction of large arteries by atherosclerosis and associated thrombi, obstruction of small arteries by lipohyalinosis and associated thrombi and embolic arterial obstruction arising from atherosclerotic debris from arteries in the chest or neck, or from thrombi in the heart. Rothrock believes we can tell one type from the other. I am less certain. The approach he outlines to making these distinctions is valid but it often falls far short. Once a fixed deficit appears—that is, an ischemic stroke occurs—it is more often possible to be certain, but even at autopsy one often cannot be certain of the pathophysiology. Nevertheless, it seems likely that the best treatments for the various causes of TIA will be different and that we must make as specific a diagnosis as possible when confronted with the "TIA syndrome" if we are to initiate appropriate specific treatment.

Again, Rothrock expresses concern that "much of our failure to show real benefit from various treatments for TIA and stroke has resulted from the tendency to 'lump together,' to regard TIA and stroke as diagnoses per se and not as syndromes with diverse causes." This may be true. It has been a major criticism of the extracranial-intracranial bypass study.[1] It seemed a few years ago (and still does!) to make excellent sense to take patients with cerebral ischemic symptoms and an inoperable obstruction in the carotid arterial system, and bypass the obstruction. Consequently, a large, multicenter study was carried out to determine if the operation is effective in preventing strokes in patients with recent hemispheric or retinal TIA or infarction who had atherosclerotic narrowing or occlusion of the ipsilateral internal carotid or middle cerebral artery. The study involved 1,377 patients randomly selected to "best medical care" (which included one aspirin given four times a day) versus "the same regimen plus bypass surgery joining the superficial temporal artery to the middle cerebral artery" and followed for an average of 56 months. The study methods were impeccable and the results were definitive. The operation failed to reduce the risk of ischemic stroke. Subsequently, it has been emphasized[2] that positron emission tomography has the ability to separate patients with symptomatic cerebral ischemia into three pathophysiologic states: those with (1) normal cerebrovascular physiology, (2) exhausted hemodynamic reserve and (3) impaired oxygen carriage reserve. Some hopeful investigators believe that revascularization applied to those patients with demonstrated hemodynamic impairment, rather than those selected on the less discriminatory clinical grounds that were used in the extracranial-intracranial bypass study, will prove to be beneficial. I doubt they are correct—but for several million dollars we could find out! It is true that several kinds of patients were lumped together in this study and randomization by the positron emission tomography strata noted above may have yielded different results—although analysis for a large number of theoretically important variables failed to show any group of patients who benefited from the surgical procedure. I am not criticizing the importance of randomly selecting patients by accurate and specific diagnoses, but many preconceived ideas are often incorporated in the "correct diagnosis."

I am less pessimistic that "aggressive treatment of a patient with [TIA] has little effect on reducing stroke incidence." I believe the weight of evidence favors the view that aspirin works! The question is how well, in whom and in what dose. Aggregate data[3] indicate that 1,300 mg given daily reduces the incidence of stroke by about 25% in men with TIA of recent onset or small stroke, and we will likely learn soon that 325 mg is equally as effective.[4] It appears to benefit women less, if at all. Sulfinpyrazone (Anturane) and dipyridamole have not proved effective in preventing atherothrombotic stroke.[4] Ticlopidine hydrochloride is a new plate-